The Treatment of Cancer of the Thyroid Gland

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• **The optimum treatment for cancer of the thyroid depends on (a) the pathological type of tumor present and (b) the stage of the disease.**

In patients with well-differentiated papillary carcinoma, simple operation is usually adequate. In cases of most other types, more extensive operation, followed by adequate postoperative radiotherapy, is regarded as the treatment of choice. In terms of clinical stage, the primary treatment of most cases classified as Stage I or II should be surgical, and of most cases classified as Stage III or IV, radiological.

The five-year survival rate in a series of non-terminal cases treated under such a program was 47 per cent.

Persistent treatment of selected inoperable or metastatic lesions may result in unexpectedly long survivals.

CARCINOMA of the thyroid gland is relatively uncommon. According to the most recent available statistics reviewed by Dorn and Cutler,[6] the age adjusted incidence of cancer of the thyroid gland in the United States each year is approximately 1.1 per 100,000 males and 3.4 per 100,000 females. In other words the incidence is about 2.3 cases per 100,000 population per annum. Sokal,[14] after an extensive review, also estimated the incidence at approximately this figure.

The usual sex ratio of thyroid cancer is three cases in females for every one in males.

In adults with nodular goiter the incidence of thyroid cancer is stated at widely different rates, ranging from about 0.2 per cent of patients with nodular goiter according to Sokal, through 4.8 per cent of such patients according to Queen,[13] up to as high as 20 per cent according to some surgical observers.[15] Since the latter usually base their data largely on patients operated upon, while other investigators use data based on a theoretical "total" population sample, it would appear that the true incidence of thyroid cancer in all adults with nodular goiter is distinctly less than four per cent. Sokal expressed belief that thyroid cancer arises more frequently in toxic than nontoxic nodular goiter (the respective percentages being 1 and 0.2). Other observers do not concur. There has been a considerable divergence of opinion as to the incidence of cancer with regard to whether there is a solitary nodule or multiple nodules on the thyroid gland. However, since surgical and microscopic examination of thyroid glands with so-called solitary nodules usually reveals the presence of additional or multiple nodules, this aspect of the problem will not be considered further herein.

The incidence of thyroid cancer in children with nontoxic nodular goiter is reported by Winship[18] to be almost 30 per cent (that is, of those children coming to operation); it is presumably lower in children in general who have that disease, but the exact figure is not known.

PATHOLOGIC CLASSIFICATION

There are almost as many pathologic classifications of tumors of the thyroid gland as there are reports in the literature. For several years the rather detailed classification of Warren was commonly used. Ackerman[1] modified Warren's classification essentially as follows:

I. Tumors of low or potential malignancy.
   1. Adenoma with blood vessel invasion (fetal adenoma).
   2. Papillary cystadenoma with blood vessel invasion.

II. Moderate degree of malignancy.
   1. Papillary adenocarcinoma.
   2. Alveolar adenocarcinoma.
   3. Hurthle cell adenocarcinoma.

III. Higher grade malignancy.
   1. Small cell carcinoma (carcinoma simplex).
   2. Giant cell carcinoma.

IV. Miscellaneous types.
   1. Epidermoid carcinoma.
   2. Fibrosarcoma.
   3. Lymphoma.

Bell[2] and others stressed the fact that there are no dependable microscopic criteria for the diagnosis of malignant adenoma. Bell noted that some investigators observed that malignant adenoma recurs in only about 3 per cent of cases even though the tumor may have invaded veins.

In recent years there has been a tendency to classify carcinomas of the thyroid gland as follows:

1. Papillary adenocarcinoma (tumors with papillary or predominantly papillary pattern). Many of these are well differentiated.

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2. Follicular adenocarcinomas (tumors with follicular or predominantly follicular pattern — formerly called alveolar).

3. Undifferentiated carcinoma (including tumors which formerly carried such headings as small cell, giant cell, spindle cell and solid carcinomas).

There are of course other primary malignant lesions of the thyroid gland such as epidermoid carcinoma, oxyphilic (or Hurthle cell) carcinoma, malignant lymphoma and sarcoma. These are relatively uncommon. In addition, there are malignant tumors metastatic from other sites, notably the breast and lung, which may be mistaken clinically for primary thyroid cancer even by the most wary.

The approximate incidence of the different pathologic types varies in different reported series. In general, it would appear that tumors of low grade malignancy constitute about 55 per cent of malignant thyroid tumors; those of moderately good differentiation, including follicular tumors, average perhaps 30 per cent of all thyroid cancers, while those of undifferentiated type or high degree of malignancy average about 15 per cent. It is noteworthy that in reports from some surgical clinics, the undifferentiated group accounted for less than 8 per cent of the series treated, while in reports from some radiotherapeutic clinics this undifferentiated group accounted for as high as 51 per cent of the cases treated. It is therefore evidently impossible to compare the overall results of treatment in different institutions in the absence of knowledge of the relative number of the different pathologic types treated.

Winship and Chase[18] recorded the following pathologic types in a collected series of 596 cases in adults studied in recent years (they are listed in the order of increasing malignancy):

Cell Type	Per Cent
Papillary adenocarcinoma	15
Papillary and follicular adenocarcinoma	46
Follicular adenocarcinoma	17
Oxyphilic adenocarcinoma	3
Undifferentiated adenocarcinoma	18
Lymphoma	1

In about two-thirds of the mixed papillary and follicular tumors, the papillary type predominated; in the other one-third, the follicular type (which sometimes accepts therapeutic amounts of radioiodine) predominated.

STAGING

Clinical staging of tumors has moderate value both for the planning of treatment and for the estimation of prognosis, notably in the case of cancers of the uterine cervix and the breast. Staging based on clinical and microscopic observations is of value in dealing with tumors of other sites such as the fundus uteri. There is considerable divergence of opinion in the literature as to the value of staging in thyroid cancer. Some investigators, Winship[18] among them, regard staging as of more importance than the histologic type in estimating prognosis; other observers have the opposite opinion, Jacobsson[8] proposed the following staging based on the clinical and microscopic observations at the time of surgical exploration carried out in patients with thyroid "lumps":

1. Movable tumor without known metastasis.

2. Movable tumor, with mobile unilateral node metastasis.

3. Fixed tumor, or tumor with bilateral or fixed node metastasis.

4. Patient with distant metastatic lesions.

The limitations of either microscopic or macroscopic staging is well illustrated by Ward's[16] prognostic summary:

Five-year survival rates based on clinical and surgical observations:

	Per Cent
1. Carcinoma diagnosed or suspected preoperatively	20
2. Carcinoma diagnosed at operation (gross)	40
3. Carcinoma diagnosed first on microscopic examination	80

Kearns and Davis[9] expressed belief that the histologic appearance of the tumor contributes little to the prognosis. All agree that some relatively well differentiated papillary tumors progress to a fairly early fatal outcome, while occasional undifferentiated tumors are associated with unexpected longevity. Crabtree and Hunter[4] said that "Deaths from cancer of the thyroid are directly proportional to the ease of clinical diagnosis (*i.e.* the stage) and the degree of anaplasia."

TREATMENT

The primary treatment of most cases of carcinoma of the thyroid is surgical, in order to provide both microscopic diagnosis and potential removal of the lesion. There is wide difference of opinion as to whether the operation should consist of relatively simple excision (lobectomy) or removal of the entire thyroid gland combined with radical neck dissection. Martin[10] expressed belief in the value of thyroidectomy with radical neck dissection, the latter at least on the same side as the lesion. On the other hand, Crile[5] and many equally experienced surgeons have expressed the opinion that radical neck dissection has not much to offer, pointing out that when metastasis to nodes is present in the case

of well differentiated papillary tumors, the nodes tend to grow slowly and remain with little change in size for many years. On the other hand when such metastasis is present (especially in the case of poorly differentiated tumors), the probability of the surgeon's being able to remove all the involved nodes is slight; many patients with metastasis to cervical nodes also have nodal involvement extending below the clavicle into the mediastinal or axillary areas. Surgical removal of mediastinal nodes has been attempted, but the condition of the patients after bilateral radical cervical and upper mediastinal node dissection is not a very happy one.

The general plan of treatment which the author believes to be wise may be summarized as follows (utilizing the previously described staging):

Stage I and II: Usually surgical. Then, if the tumor is microscopically well differentiated and apparently totally removed, no postoperative radiotherapy; but if the tumor is poorly differentiated or incompletely removed: radiotherapy.

Stage III and IV: Usually radiotherapy (after confirmation of diagnosis).

In general, the most effective way of irradiating the neck and adjacent tissues in the presence of inoperable carcinoma of the thyroid gland is by wide-field roentgen therapy.[12] In many cases a single large anterior field may be used, the field extending from approximately the hyoid bone down to the middle of the manubrium sterni. (The intrinsic larynx is shielded with lead.) Such a field includes both the cervical and upper mediastinal node groups. In suitably built patients, with "thick" necks, two lateral fields may be added. In selected patients, posterior oblique fields, aimed at the thyroid and its lymph node drainage area (but missing the spinal cord) may also be used.

In patients with widespread lesions of a follicular type, which accept radioactive iodine (perhaps 2.5 per cent of all patients with cancer of the thyroid gland) radioiodine should be used.

The usual plan of treatment is to attempt to deliver a midtumor dose of approximately 4,000 r in about four weeks, using orthovoltage radiation with a half value layer of 2 mm. copper.

It is believed that 4,000 r of 250 kilovolt radiation with the half value layer of 2 mm. of copper is biologically equivalent (in terms of effect on cancer in humans) to about 6,000 gamma roentgens from a teleradium, telecobalt or megavoltage source. Most adult patients will tolerate this dosage to a wide field in a four-week period without serious permanent after effects. If heavier dosage to large areas is given, undesirable late sequelae are likely to occur. On the other hand, sharply localized persistent areas of disease may sometimes be treated with small fields to a tumor dose of about 6,000 x-ray roentgens in four weeks, but cases suitable for such therapy are exceptional.

The radiosensitivity of thyroid cancer in the individual case cannot be predicted. It can only be determined by a trial of adequate radiotherapy. In general, it would appear that:

1. Most tumors of predominantly papillary type are moderately radiosensitive;

2. Tumors of predominantly follicular type are radiosensitive in about one-half the cases; and

3. Tumors of undifferentiated type are usually radiosensitive, but unfortunately incurable because of early generalized metastasis.

Metastatic disease in the lungs, bones, brain and distant node sites may be treated by roentgen therapy or radioiodine according to the nature of the case and the presence or absence of iodine-accepting tumor tissue. Unfortunately, only the adenocarcinomas with colloid formation (follicular tumors) take up enough radioiodine to be affected significantly, and even those that do accept the iodine do not take it up homogeneously.[11]

In general, only about 50 per cent of patients with cancer of the thyroid gland have "operable" lesions when first observed (Cohen and Moore),[3] and since it is exceptional to be reasonably sure that all of the tumor has been excised, careful postoperative radiotherapy should be carried out in most "operable" cases. The kind of tumor present is probably more important in the determination of ultimate survival than the extent of the operation or the intensity of the radiotherapy applied.

RESULTS OF TREATMENT

The author's personal experience with cancer of the thyroid gland is small: Between the years 1930 and 1952, 23 patients were observed in consultation at the San Francisco Hospital and 19 patients in private practice, a total of 42 cases of "validated" cancer of the thyroid gland.

The pathological classification and clinical staging of the patients were not uniform during this period. Indeed, there were 31 cases indexed as *carcinoma of the thyroid* in the San Francisco Hospital files up to 1952, but upon review it was noted that in eight of the cases the patient did not have primary thyroid cancer. These eight were as follows:

Carcinoma of the thyroid gland, metastatic from lung, one case.

Carcinoma of the thyroid gland, metastatic from an undetermined primary site, three cases.

Adenoma benign (reviewed diagnosis), two cases.
Error in tumor registry, two cases.

These eight cases are not included in the subsequent discussion.

The pathological classification employed at the time of preparation of this summary was as follows:

1. Papillary carcinoma and other well differentiated tumors (such as so-called malignant adenoma).

2. Adenocarcinoma, unspecified or moderately well differentiated.

3. Undifferentiated carcinoma (and carcinoma, type unspecified).

It is now apparent that this classification is neither as clear nor as logical as that listed previously in this paper. However, it will be used in presenting the results to date.

The staging was based on that of Jacobsson and was done retrospectively after a review of the clinical, surgical and microscopic records.

The treatment consisted of surgical operation alone in the cases of papillary tumors which had been apparently completely removed, of operation plus postoperative roentgen therapy in the other operable cases, and of radiotherapy alone in the nonterminal inoperable cases. The surgical operation was usually conservative (lobectomy). In some cases it consisted of biopsy only; in others, total thyroidectomy was done. The postoperative radiotherapy was moderately intensive in patients whose clinical condition permitted (the aim being to give a midtumor dose of about 4,000 x-ray roentgens in some four weeks' time). It was usually merely palliative or even only token in amount in the advanced or terminal cases.

Of the 14 patients known to have survived over five years, 11 received postoperative radiotherapy.

Of the 28 patients who did not survive five years (including the three cases in which follow-up information is not available), 15 received postoperative radiotherapy. Many of the group who did not receive treatment were in terminal stage. Some of them had little more than biopsy or tracheotomy.

Of the 15 adequately followed patients who were not in terminal condition when first observed, 11 received postoperative radiotherapy and four did not. The average survival time in both groups was quite similar (about 22 months) despite the fact that the patients given radiotherapy were a much less favorable group. Most of the patients referred for postoperative radiotherapy had obvious persistent or inoperable tumor; two of the four not referred were believed to have had successful removal of tumor, and the other two were found to have widespread metastatic lesions shortly after operation. Objective evidence of radiotherapeutic benefit included shrinkage of palpable masses, improvement in swallowing and decrease in size of radiographically visible lesions. The most frequent reason for ultimate failure was the undifferentiated nature of the tumor present.

Pathological classification of cases:

Type (see text)	San Francisco Hospital	Private Office	Total
Papillary carcinoma	5	6	11
Adenocarcinoma	4	5	9
Undifferentiated carcinoma	14	8	22

Clinical staging of cases:

Stage	San Francisco Hospital	Private Office	Total
I	4	2	6
II	2	7	9
III	5	7	12
IV	12	3	15

Record is available of 39 of the 42 patients either to death or for over five years. The three untraced patients are counted as dead of disease in the final tabulation, although in two of them the disease was classified as Stage I and they were living and well some years (but less than five years) after operation. In the other patient lost to follow-up before a full five years had elapsed, the classification was Stage II.

The five-year survivals according to pathologic type are as follows: Papillary carcinoma, eight of eleven patients; adenocarcinoma, moderately differentiated, two of nine cases; carcinoma, undifferentiated or unspecified, four of twenty-two cases.

It is known that long survivals in undifferentiated carcinoma of the thyroid gland are so rare as to raise reasonable doubt concerning the pathological classification of such cases. Only one of the four patients in this small series who survived for such a period had a diagnosis of undifferentiated carcinoma; the remaining three had unspecified or unclassified carcinomas, without clear information as to the predominant type of cell present.

The five-year survivals according to the clinical and microscopic stage of disease were as follows:

Stage I: Four of six patients are known to have survived; (two not traced).

Stage II: Six of nine patients are known to have survived; (one not traced).

Stage III: Four of twelve patients survived.

Stage IV: None of 15 patients.

It should be noted that two of the patients died not of thyroid cancer but of cardiac disease. However, they died within the five-year interval and theoretically might have had recurrence had they lived. Conversely, two of the patients who did survive five years, had recurrence after that time (one at six and one at seven years) and died of cancer.

In all, 14 of 42 patients (33 per cent) survived five years. Twelve of the 42, were actually in terminal condition on admission and died of cancer within a few weeks. Excluding this hopeless group (to which neither curative operation nor radiotherapy was applicable) 14 of 30 patients survived five years (47 per cent).

As was previously noted, three of these survivors were treated by surgical operation alone and 11 by operation and radiotherapy. The three treated by operation alone were as follows:

1. A man 40 years of age. Subtotal thyroidectomy for papillary adenocarcinoma (pathologically, malignant adenoma). No postoperative roentgen therapy. After five years recurrence developed in neck and then bony metastasis. Palliative roentgen therapy was given. The patient died in the sixth postoperative year.

2. A 65-year-old woman. Thyroidectomy for "malignant adenoma" with capsular invasion. Later pathologic diagnosis: Papillary adenocarcinoma. Postoperative roentgen therapy advised, but patient was discharged before it was administered. Living to date (five years).

3. A woman 49 years of age. Hemithyroidectomy for moderately differentiated adenocarcinoma. No postoperative roentgen therapy. After three years questionable scapular metastasis developed. Radiotherapy was given. Living five years postoperatively.

PROGNOSIS

Prognosis in individual cases of cancer of the thyroid gland is difficult. Kearns[9] reported a patient who had thyroid carcinoma for 35 years yet was clinically well. Crile[5] noted a similar case. The patient was well for over 25 years without treatment. The diagnosis was made by cervical node biopsy. Ward[15] reported a patient who had goiter at age 24. It was present for 26 years before operation, was resected three times and treated with radiotherapy, and finally caused death at age 68. Ward asked: "Was the tumor malignant for 44 years, or for only about 20 years?"

One of the patients in the present series, a woman 22 years of age with undifferentiated carcinoma of the thyroid gland, had subtotal thyroidectomy (the clinical diagnosis was thyroiditis or "Hashimoto struma"). Two experienced pathologists interpreted the removed gland as undifferentiated carcinoma. The surgeons suspected that they had "seeded" the neck area and that reoperation would be futile. An immediate postoperative course of roentgen therapy to a tissue dose of approximately 4,000 r in four weeks was given. It was the author's impression and that of the surgeons that the prognosis was hopeless. However, when last observed six years later, the patient, the mother of two children, was clinically well and without evidence of tumor or undesirable skin changes. Hers is regarded as an exceptional case.

In general, there is good prognosis for long survival with well-differentiated papillary adenocarcinomas, but startling exceptions do occur, and "indolent" tumors may become aggressive, especially in metastatic lesions.

With undifferentiated carcinoma of the thyroid gland the prognosis is virtually hopeless. Most patients are dead within a year of histological recognition.

Tumors of moderate differentiation are often associated with long survival especially when vigorous surgical and radiological means are employed to control the various manifestations of the disease as they appear. Diffuse pulmonary and nodal metastatic lesions may prove sensitive to roentgen therapy; bone lesions frequently heal; persistent efforts by the attending physician may yield great dividends in cases of this type. Radioiodine may occasionally be of much help.

MORBIDITY OF RADIOTHERAPY

Radiotherapy, like surgical treatment has its morbidity. With care and experience this can be kept to a minimum. It includes early erythema and dysphagia, and late telangiectasis, atrophy, fibrosis and ulceration. More serious complications include fistula and hemorrhage. Surgical morbidity includes bilateral recurrent laryngeal paralysis, postoperative hemorrhage, hypoparathyroidism, esophageal fistula and severe debility (which sometimes follows ultraradical procedures). Radical radiotherapy is rarely feasible or wise after radical operation.

Late undesirable radiotherapeutic effects can be kept to a minimum by careful individualization of treatment, avoidance of unduly rapid dosage, especially in the presence of infection, and scrupulous attention to technical details. When the radiotherapist himself performs each irradiation procedure he is in the best position to individualize carefully. Unduly protracted courses of irradiation, repeated heavy irradiation, and too rapid dosage in the case of debilitated persons all should be avoided.

In selected cases, ultra-hard radiation may be indicated. However, devices such as convergent beam therapy, rotation therapy, grid therapy and attempted tumor sensitization with drugs like synkavit have not been reported as effective.

DISCUSSION

The optimum place of radiotherapy in the treatment of cancer of the thyroid gland is the subject of considerable controversy. Most surgeons appear to agree with Martin[10] that it is indicated for "rapidly growing, inoperable, and locally recurring thyroid cancer" and for "painful osseous metastases"; but several add the comment that its postoperative use is not usually indicated. This paradox is presumably owing to the fact that much surgical writing deals with the operable cases in which *all* the tumor has been apparently removed, the writer ignoring or forgetting the many cases in which it is unfortunately not possible to dissect all the tumor from the trachea or remove all of the involved nodes.

Martin objected that "no evidence has ever been presented that radiation alone has produced five-year cures of thyroid cancer," apparently ignoring the five-year survivals in inoperable cases reported by Windeyer,[17] Jacobsson,[8] Paterson[12] and others. These five-year survivals in good health are just as much clinical cures as five-year survivals after surgical operation alone. In both instances, many of the patients would probably have survived five years anyway—because of the biological type of cancer present. However, in some cases the definitive radical therapy (radiological or surgical) unquestionably removed or destroyed hazardous masses. The author believes that except in the case of well differentiated papillary tumors apparently completely excised, the weight of clinical evidence is in favor of postoperative radiotherapy.

Survival or cure rates are always difficult to analyze. Most reports of surgical results are based on the operable cases seen and followed; they are relative, not absolute, results, and often exclude patients with inoperable lesions, those who refuse operation, those who died of intercurrent disease within five years and those who were lost to follow-up. Reports of radiotherapy results tend to be based on patients who were inoperable at the time of diagnosis or in whom the surgeon felt that some tumor had been left behind. They are strictly not comparable with surgical results in the more favorable series of operated cases. However, as in the case of surgical reports, some radiotherapists exclude cases in which the patient died of intercurrent disease or in whom completion of treatment was not possible, and few published results are "absolute"—that is, based on all patients seen, whether treated or not.

Recurrences may appear after such long periods of quiescence that Winship and Chase,[18] for example, would prefer results to be based on 20-year follow-up. They therefore disagree with Martin in his rather astonishing observation that "To be of practical value, end results . . . cannot very well be calculated on the basis of an observation period of much more than 5 years—otherwise by the time the figures were calculated, a great proportion of the active surgeons would have died of old age or be in retirement, in which case few surgeons could improve their methods by a critical analysis of their own experience and results."

Horn and Dull[7] noted that five-year survival of 59 per cent (of 112 cases) dwindled to ten-year survival of only 30 per cent—and three of the latter group of patients had known recurrent disease. It is to be noted that in two-thirds of the cases in the group reported upon, the lesions were detected microscopically. The five-year survival rate for the patients in whom cancer was diagnosed clinically was only 37 per cent.

The following are other recently published five-year survival rates:

Windeyer[17] (London University-Middlesex Hospital): 37 per cent.

Cohen and Moore[3] (University of Minnesota)*: 34 per cent.

Jacobsson[8] (Radiumhemmet, Stockholm): 46 per cent.

Martin[10] (Memorial Hospital, New York): 42 per cent.

On the other hand (and to illustrate the results obtainable with material doubtless less favorable than the above) Watson and Pool[16] reported five-year survival of only eight per cent. Presumably their series contained a much larger proportion of cases of undifferentiated or advanced cancers than those of the other quoted investigators whose papers were published in more recent years.

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